

Minireview

Galectin-I as a potential cancer target

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Galectins are a family of structurally related carbohydrate-binding proteins, which are defined by their affinity for poly-*N*-acetyllactosamine-enriched glycoconjugates and sequence similarities in the carbohydrate recognition domain. Galectin-I, a member of this family, contributes to different events associated with cancer biology, including tumour transformation, cell cycle regulation, apoptosis, cell adhesion, migration and inflammation. In addition, recent evidence indicates that galectin-I contributes to tumour evasion of immune responses. Given the increased interest of tumour biologists and clinical oncologists in this field and the potential use of galectins as novel targets for anticancer drugs, we summarise here recent advances about the role of galectin-I in different events of tumour growth and metastasis.

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Classification and carbohydrate specificity

Galectins are animal lectins defined by shared consensus amino acid sequences and affinity for β -galactose-containing oligosaccharides (Leffler *et al*, 2004). Members of the galectin family are composed of one or two carbohydrate-recognition domains (CRDs) of approximately 130 amino acids. Regarding the biochemical structure, some galectins contain one CRD and exist as monomers (galectin-5, -7 and -10) or dimers (galectin-1, -2, -11, -13, -14 and -15), whereas other galectins such as galectin-4, -6, -8, -9 and -12 contain two CRDs connected by a short linker region. In contrast, galectin-3 uniquely occurs as a chimeric protein with one CRD and an additional nonlectin domain, which is involved in the oligomerisation of this protein. It has been suggested that multivalency of individual members of the galectin family and their crosslinking properties might determine different biological responses by inducing aggregation of specific cell-surface glycoreceptors, which – in many cases – are associated with different signal transduction events (reviewed in Rabinovich *et al*, 2002a).

The first discovered protein in the family was galectin-1, a noncovalent dimer composed of subunits with one CRD. Although this protein binds preferentially to glycoconjugates containing the ubiquitous disaccharide *N*-acetyllactosamine (Gal β 1-3/4 GlcNAc), binding to individual lactosamine units is of relatively low affinity and it is the arrangement of lactosamine disaccharides in repeating chains (polylactosamine) that increases the binding avidity (Schwarz *et al*, 1998; Ahmad *et al*, 2004).

Subcellular distribution

Galectin-1 lacks recognisable secretion signal sequences and does not pass through the standard ER/Golgi pathway (Leffler *et al*, 2004). In addition, it shows characteristics of typical cytoplasmic proteins, including acetylated *N*-terminus and lack of glycosylation. However, there is evidence that this protein, as well as other members of the galectin family, is secreted by a novel mechanism distinct from classical vesicle-mediated exocytosis.

Regulated expression of galectin-1 in tumours

Detailed description of the expression and functional status of galectins in different tumour types has been recently provided (Danguy *et al*, 2002; Nangia-Makker *et al*, 2002; van den Brule *et al*, 2003; Lahm *et al*, 2004; Liu and Rabinovich, 2005). Here we will review the role of galectin-1 in different steps of tumour progression to evaluate its potential use as a therapeutic target in cancer.

Expression of galectin-1 has been well documented in many different tumour types including astrocytoma, melanoma and prostate, thyroid, colon, bladder and ovary carcinomas (reviewed by Danguy *et al*, 2002). Interestingly, in most cases such expression correlates with the aggressiveness of these tumours and the acquisition of metastatic phenotype. Whether expression of galectin-1 in tumour tissue or tumor-associated stroma may actively influence disease outcome still remains to be elucidated.

GALECTIN-1 AND TUMOUR TRANSFORMATION

It has been recently demonstrated that intracellular galectin-1 may play a key role in the initiation of transformed phenotype of tumours. Kloog and colleagues have found that galectin-1 interacts with oncogenic H-RAS and contribute to membrane anchorage of H-RAS (Paz *et al*, 2001). Interestingly, overexpression of galectin-1 in tumour cells results in an increase in both the membrane association of H-RAS and cell transformation.

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GALECTIN-1 IN TUMOUR GROWTH

Over the past few years, the perceived role of galectin-1 in tumour growth has mirrored the story of Dr Jekyll and Mr Hide. While the endogenous protein may function as a growth-promoting factor, exogenously added galectin-1 specifically suppresses tumour cell proliferation. In this sense, Yamaoka *et al* (2000) showed that inhibition of *gal-1* gene expression in a rat glioma cell line arrests tumour growth, suggesting that endogenous galectin-1 has growth-promoting activity. On the other hand, Kopitz *et al* (2001) showed that exogenously added galectin-1 inhibits the growth of neuroblastoma cells. Thus, the effects of galectin-1 appear to be multifaceted. It can function in both carbohydrate-dependent and independent manners and its effects can be either positive or negative, depending on the responder cell types or its subcellular localisation. Interestingly, it has been reported that galectin-1 exerts a biphasic modulation of cell growth. While high doses of galectin-1 inhibit cell proliferation independent of its sugar-binding activity, low doses of galectin-1 are mitogenic and are susceptible to inhibition by lactose (Adams *et al*, 1996). Furthermore, galectin-1 can also regulate cell cycle progression in human tumour cells (Wells *et al*, 1999).

GALECTIN-1 AND THE TUMOUR MICROENVIRONMENT

Tumour metastasis is a multistep process that includes changes in cell adhesion, increased invasiveness, angiogenesis and evasion of the immune response. Galectin-1 has been shown to contribute to all these processes (Figure 1).

Galectin-1 and cell adhesion

The metastatic cascade involves many changes in cell-cell and cell-extracellular matrix (ECM) interactions, and these include the detachment of cells from the primary tumour and their attachment to ECM proteins at distal sites. As they can bind to extracellular glycoconjugates, galectins might modulate the adhesion between adjacent cancer cells or between cancer cells and ECM. It has been shown that galectin-1 increases the adhesion of prostate and ovarian cancer cell lines to the ECM (Ellerhorst *et al*, 1999; van den Br le *et al*, 2003). In addition, galectin-1 can also mediate homotypic cell aggregation of human melanoma cells in a carbohydrate-dependent manner (Tinari *et al*, 2001).

Galectin-1 and the control of cell migration

Galectin-1 has been shown to affect cell migration of tumours and influence their invasiveness. In fact, exogenously added galectin-1

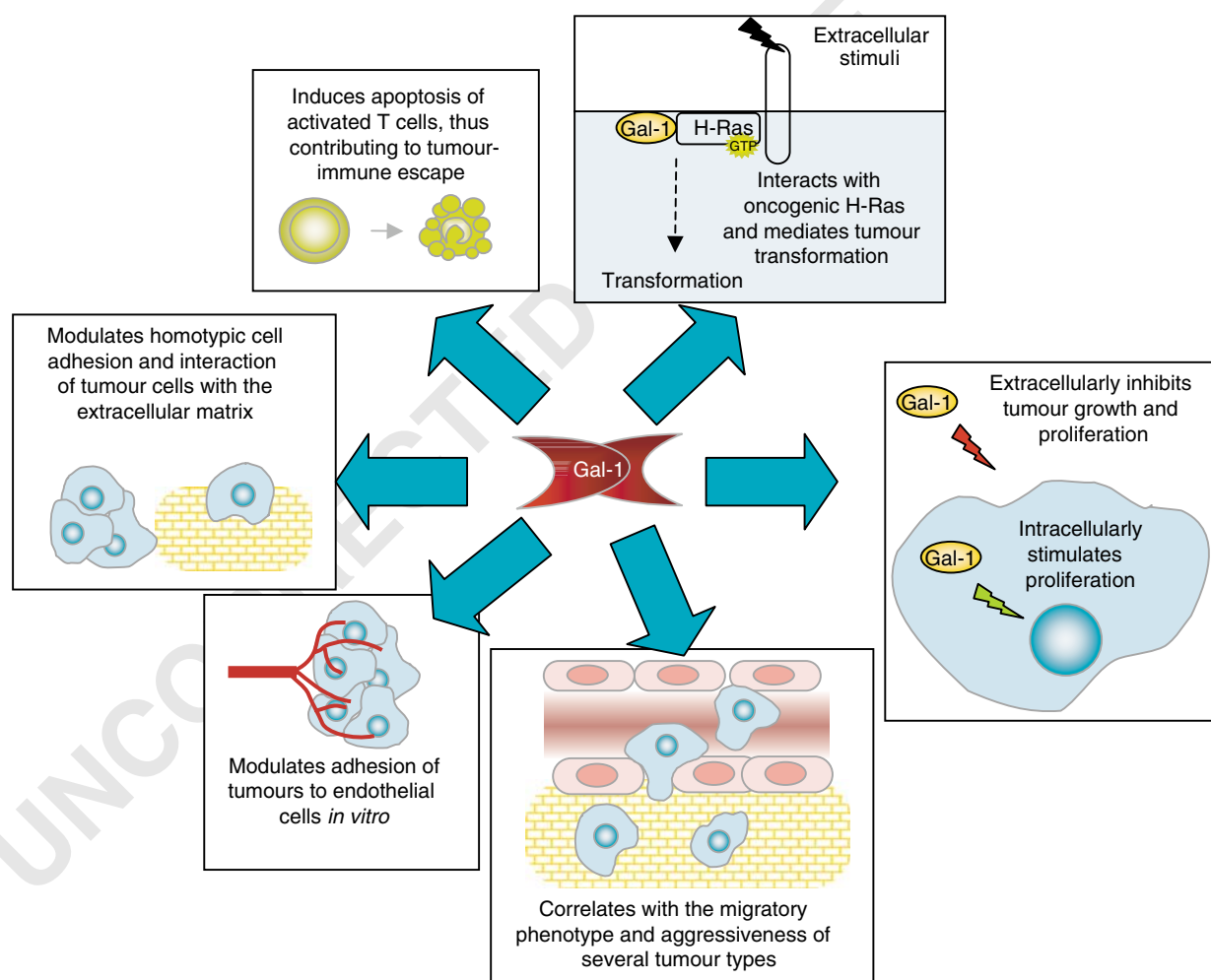


Figure 1 Contribution of galectin-1 to tumour progression. Galectin-1 interacts with oncogenic H-RAS and contributes to membrane anchorage of H-RAS and tumour transformation. In addition, this protein modulates cell growth, cell adhesion and cell migration, thereby affecting the process of tumour metastasis. Furthermore, recent evidence indicates that tumour cells secrete substantial levels of galectin-1 to evade T-cell-mediated responses.

causes increased motility of glioblastoma cells *in vitro* (Camby *et al*, 2002). Although the precise mechanisms have not yet been elucidated, it is possible that galectin-1 may engage cell surface glycoproteins involved in cell motility. In addition, Clausse *et al* (1999) showed that this protein is upregulated in capillaries associated with carcinoma cells and can mediate interactions between tumours and endothelial cells *in vitro*, suggesting a potential role for galectin-1 in modulating angiogenesis.

GALECTIN-1, INFLAMMATION AND ANTITUMOUR RESPONSES

Chronic inflammation is considered to be one of the most important factors contributing to tumour progression. Although the immune system can reduce tumour incidence through immune-surveillance mechanisms (Dunn *et al*, 2004), it can also promote tumour progression through inflammation-dependent mechanisms (Lin and Pollard, 2004). Galectins are expressed by many different inflammatory cells and regulate the function of these cells (Rabinovich *et al*, 2002a). In addition, galectins are released by tumours and can positively or negatively influence a variety of inflammatory responses.

Galectin-1 and the inflammatory response

Undoubtedly, the most studied function for galectin-1 is related to the regulation of the inflammatory response. In recent years, it has become increasingly clear that galectin-1 can function as a homeostatic agent by modulating innate and adaptive immune responses. Galectin-1 induces cell growth inhibition, inhibits T-cell activation and promotes apoptosis of activated T cells (Perillo *et al*, 1995; Blaser *et al*, 1998; Rabinovich *et al*, 1998; Chung *et al*, 2000). Furthermore, we have recently shown that galectin-1 sensitises resting T cells to CD95/Fas-mediated cell death (Matarrese *et al*, 2004).

One concern regarding the proapoptotic activity of galectin-1 is that this effect has been demonstrated in most cases at relatively high concentrations (micromolar range) and it is uncertain whether high levels of soluble protein can be achieved *in vivo*. Interestingly, recent evidence indicates that the amount of galectin-1 secreted by different cell types is sufficient to kill T cells, when galectin-1 is presented in the context of the ECM (He and Baum, 2004).

Different cell surface glycoconjugates on the surface of activated T cells appear to be primary receptors for galectin-1, including CD45, CD43 and CD7 (Pace *et al*, 1999). Interestingly, galectin-1 binding to T cells results in marked redistribution of many of these glycoreceptors into segregated membrane microdomains. It has been demonstrated that the regulated expression of glycosyltransferases during development and activation, creating *N*-acetylglucosamine ligands, may determine T-cell susceptibility to galectin-1-induced cell death (Galvan *et al*, 2000; Amano *et al*, 2003).

As previously mentioned, CD7 has been identified as a critical receptor for galectin-1-induced apoptosis, and it has been recently demonstrated, that CD7⁺ T cells from patients with mycosis fungoides/Sezari syndrome are protected from galectin-1-mediated apoptosis (Rappl *et al*, 2002; Roberts *et al*, 2003).

The signal transduction events leading to galectin-1-induced apoptosis involve several intracellular mediators of apoptosis in primary T lymphocytes, including the induction of specific transcription factors, activation of caspases, cytochrome *c* release and participation of the ceramide pathway (Rabinovich *et al*, 2000a; Matarrese *et al*, 2004). However, a recent study showed that apoptosis induced by galectin-1 in a T-cell line is not dependent on the activation of caspase-3 or on cytochrome *c* release (Hahn *et al*, 2004). Furthermore, Dias-Baruffi *et al* (2003) reported that galectin-1 can induce the exposure of phosphatidylserine (an early

apoptotic marker involved in the phagocytosis of apoptotic cells) on the plasma membrane of human T leukaemia cells and neutrophils, but this event does not result in DNA fragmentation. Thus, galectin-1 might activate different death pathways or different apoptosis end points in different cell types.

The pathophysiological relevance of galectin-1-induced cell death has been demonstrated in experimental models of chronic inflammation, including collagen-induced arthritis (Rabinovich *et al*, 1999b), inflammatory bowel disease (Santucci *et al*, 2003) and graft-versus-host disease (Baum *et al*, 2003). Interestingly, administration of galectin-1 *in vivo* suppresses Th1-dependent responses in these murine models and increases T-cell susceptibility to activation-induced cell death.

While relatively high concentrations of galectin-1 are required to promote T-cell apoptosis, we have demonstrated that galectin-1 at low concentrations (nanomolar range) provides a stop signal for T-cell adhesion to ECM and abrogates the production of proinflammatory cytokines, such as tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) by activated T cells, with no evidence of T-cell apoptosis (Rabinovich *et al*, 1999a). This observation supports the concept that this protein might also exert its anti-inflammatory effects through alternative nonapoptotic mechanisms. In addition, galectin-1 can also modulate acute inflammatory processes (Rabinovich *et al*, 2000b; Almkvist *et al*, 2002).

Galectin-1 and tumour-immune escape

Despite the existence of specific T lymphocytes recognising tumour cells, the impact of these cells in tumour growth has been so far elusive. In contrast, several mechanisms have been described that potentially contribute to tumour cell evasion of the immune response (Dunn *et al*, 2004). These include the production of immunosuppressive cytokines and other soluble factors, including transforming growth factor- β (TGF- β), interleukin 10 (IL-10) and vascular endothelial growth factor (VEGF).

The immunoregulatory effects of galectin-1 and the correlation between galectin-1 expression in cancer cells and the aggressiveness of these tumours prompted us to investigate the role of galectin-1 in tumour-immune escape. We hypothesised that tumour cells may impair T-cell effector functions through secretion of galectin-1 and that this mechanism may contribute in tilting the balance towards an immunosuppressive environment at the tumour site. By a combination of *in vitro* and *in vivo* experiments using knockdown transfectants, we established a link between galectin-1-mediated immunoregulation and its contribution to tumour-immune escape (Rubinstein *et al*, 2004). Blockade of the inhibitory effects of galectin-1 within tumour tissue resulted in reduced tumour mass (an effect which required intact CD4⁺ and CD8⁺ T-cell responses) and stimulated the generation of a tumour-specific T-cell response *in vivo*. Our observations support the idea that galectin-1 may contribute to immune privilege of tumours by modulating survival or polarisation of effector T cells, and suggest a potential molecular target for manipulation of T-cell apoptosis with potential implications in immunotherapy.

GALECTIN-1 AS A TARGET FOR ANTICANCER AGENTS: CONCLUSIONS AND PERSPECTIVES

Given the contribution of galectin-1 to tumour growth and metastasis, it is predicted that inhibitors of galectin-1 will find their way into cancer clinical trials, leading to delays in tumour progression and improvements in overall survival. Challenges for the future will be to employ potent and selective small inhibitors of galectin-1 and, in fact, molecules with such properties have already been developed for galectin-1 or other galectins (Andre *et al*, 2001; Sorme *et al*, 2002). Furthermore, galectin-1 expression can be

modulated by chemotherapeutic and antimetastatic agents (Lu *et al*, 2000; Rabinovich *et al*, 2002b). A current challenge is the design of more specific and potent galectin-1 inhibitors for therapeutic purposes with no or minimal adverse effects. Although galectin-1 still remains elusive in terms of our understanding of its multifunctional modes of action, we are moving ever closer to unravelling this mystery at a molecular level and to design new therapeutic approaches directed toward modulating its activities.

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